OBJECTIVES: Genetic programming is an Evolutionary Computing technique, inspired by biological evolution, capable of discovering complex non-linear patterns in large datasets. Despite the potential advantages of genetic programming over standard statistical methods, its applications to survival analysis are at best rare, primarily because of the difficulty in handling censored data. The aim of this study was to demonstrate the utility of genetic programming for the automatic development of clinical prediction models using cardiovascular disease as a case study. **METHODS:** We compared genetic programming and the commonly used Cox regression technique in the development of a cardiovascular risk score using data from the SMART study, a prospective cohort study designed to identify predictors of future cardiovascular events in patients with symptomatic cardiovascular disease. The primary outcome was any cardiovascular event, comprising cardiovascular death and non-fatal stroke and myocardial infarction. The predictive ability of the model was assessed in terms of discrimination and calibration. **RESULTS:** 3,873 patients were enrolled in the study 1996–2006, aged 19–82 years and with 460 cardiovascular events. The discrimination of both models was comparable; the C-index of the genetic programming model being smaller (0.65; 95% CI: 0.63–0.66) but not significantly different from that of the Cox regression model (0.71; 0.67–0.75). The calibration of both models was also comparable, indicating similar disagreement between observed and predicted risks. **CONCLUSIONS:** Using empirical data, we demonstrated that a prediction model developed by the novel technique of genetic programming has a comparable predictive ability to that of Cox regression. The genetic programming model was more complicated but was developed in an automated fashion and did not require the expertise needed for survival analysis. Genetic programming seems a promising technique for the automated development of clinical prediction models for diagnostic and prognostic purposes.

PRM116

IMPROVED BOOTSTRAP POINT AND CONFIDENCE INTERVAL ESTIMATION OF THE INCREMENTAL COST-EFFECTIVENESS RATIO (ICER)

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OBJECTIVES: To develop and test a novel approach to estimate the ICER via a new bootstrap approach based upon the sample coefficient of variance and optimized via computational intelligence. **METHODS:** A novel bootstrap ICER estimation approach was developed that incorporated the sample coefficient of variance to better capture information within cost-effectiveness data. In this derivation, an optimal design value parameter was also obtained via computational intelligence. Across illustrative cost and outcome correlation structures and sample sizes, a simulation study of 1111 replications with 999 bootstrap resamples each was conducted utilizing MatLab R2012b. Comparative results of point estimates versus the existing bootstrap method were presented as relative efficiencies, with 95% confidence intervals (CI) presented as coverage probability, coverage error, length, left and right bias, and relative bias. **RESULTS:** The proposed ICER yielded less statistical estimation error than the typical bootstrap approach across all cases, with the relative efficiency of point estimates ranging from +106.03% to +113.35%. An equal or improved coverage error for the CI was also consistently achieved, deviating from the population value by zero (i.e., perfect coverage) to 0.0200 versus from 0.0060 to 0.0210. Subsequently, an improved shortening of the CI length was noted. The relative bias suggested slightly more left bias and less right bias across both positive and negative cost and outcome correlation structures, reaching a maximum of 0.5238 for the proposed ICER versus 0.2222 for the usual bootstrap. **CONCLUSIONS:** This novel method to estimate the ICER via the sample coefficient of variation found improvements in the relative efficiency of point estimators and in the coverage error and length of the 95% CI across all simulated cases. Irrespective of cost and outcome correlation structure, the relative bias of this ICER suggested a slight increase in potential left-sided bias and decrease in right-sided bias versus the usual bootstrap.

PRM117

USING MULTIPLE IMPUTATION FOR MISSING VALUES TO IDENTIFY CHRONIC KIDNEY DISEASE STAGES

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OBJECTIVES: Health care researchers often encounter missing values in many datasets. Ultimately, a patient record with missing fields can still carry valuable information. This extra information becomes more important to keep in oncology and other rare disease studies where sample size is typically limited. The purpose of this study is to demonstrate that researchers can benefit from using Multiple Imputation (MI) approach to tackle missing value problems. **METHODS:** The model data from IMS claims (Dx) and retail prescription (Rx) contained year 2011 patient level CKD stage indications, longitudinal drug therapies, days of supplies, titration rates, Demographic characteristics, payment type, and physician specialties, etc. We built multivariate logistic models to identify Chronic Kidney Disease (CDK) patient stages using prescription data in order to further evaluate the prevalence, economic burden and market opportunities. Under the general assumption of missing at random (MAR), we used MI with regression method to impute the missing monotone and categorical values before the modeling process. **RESULTS:** The pooled results from 5 MI imputed datasets were reported. Compared with the results from deterministic missing imputation approach, the MI showed larger standard error and wider 95% confidence interval. The wider CI reflected the additional data uncertainty from the missing values. CDK stage 4 (11.2%) had smallest proportion and it had lowest hit rate in the prediction model. MI approach showed more CDK stage 4 identifications than those from deterministic complete case analysis. **CONCLUSIONS:** This study demonstrated that MI is capable of reflecting the underline uncertainty associated with the data by introducing random errors into the imputation process. MI can generate unbiased results and good standard error estimation when using appropriately. On the other hand, with the advent of modern computational technology, the MI becomes computationally simple and easy to use.

PRM118

IDENTIFY CHF AND COPD PAITIENTS AT HIGH RISK OF HOSPITALIZATION: USING PREDICTIVE ANALYTICS FOR PATIENT OUTREACH

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OBJECTIVES: To develop predictive models to identify CHF and COPD patients at high risk of hospitalization within the next 6 months to be used for case management outreach. **DATA SOURCES:** Data were extracted from several sources and included patient diagnoses, service utilization, lab data, and medication adherence from a large health insurance claims database, ZIP code level demographic data from the U.S. Census, patient level illness burden scores, medical episode groupers, Experian consumer and credit information, and call data between patients and customer service representatives. **STUDY POPULATION:** All commercial and Medicare members who were identified with congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) and who were continuously enrolled for at least 6 months during the model development period and 6 months during the predictive period were included. **METHODS:** Using three years of historical data from 2010 to 2012 and admissions between January and June 2013 as the target variable, the data were randomly split in half as training and validation data. The training data were used to build the predictive model. The validation data were used to evaluate model performance. Several algorithms were utilized to build predictive models: logistic regression, neural networks, and decision trees. The models were evaluated based on the lift chart and/or area under the ROC curve. The selected models were used to score data and predict future admissions. **RESULTS:** The key factors predicting admissions in the next 6 months included length of time identified with CHF and COPD, medication adherence, prior admissions, recent specialist visits, having had a customer call that mentioned 'hospital bed/hospital stay', and being on oxygen (for COPD). **CONCLUSIONS:** Four models of predicting patients at highest risk of admission have been developed, which were used to generate a list of patients with high probability of admission for case management outreach.

PRM119

AN ANALYTICAL METHOD FOR ESTIMATING THE BOUNDARIES OF AN INCREMENTAL COST-EFFECTIVENESS RATIO

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OBJECTIVES: To develop an analytical method which quantifies the reasonable limits for any incremental cost-effectiveness ratio (ICER) defined by the slope of a line connecting two points on the cost-benefit plane. **METHODS:** Assume that the ICER of a target technology vs. its comparator is defined with two points at each of which a pair of cost and benefit is given on the C(cost)-E(benefit) plane. In order to find a cost-benefit function connecting the two points, an analytical method was developed by means of curve-fitting technique with exponential and quadratic modeling. The resultant cost-benefit function was further analytically expanded to the derivative, dC/dE, we call it "tangent limit". Example calculations of the tangent limits were conducted for each model. **RESULTS:** The analytical development resulted in the following equations of the cost-benefit function and the derivative for each modeling: $C = \mathrm{Exp}((E - p)/q)$ and $dC/dE = (1/q)\,\mathrm{Exp}((E - p)/q)$ for exponential model, whilst $C = (1/q)E^2 - p/q$ and $dC/dE = 2E/q$ for quadratic model, where p and q are parameters determined by costs and benefits of the target technology and its comparator. Applying the equations for two hypothetical points, (7.6 QALY, US$100,000) and (8.6 QALY, US$150,000), we found that the ICER of 50 bounds with the lower and the upper limits, respectively, 40.6 and 60.8 US$(x1000)/QALY for exponential model, and as well, 46.9 and 53.1 for quadratic model. Those estimates were not so much different as the limits of 43.9 and 65.8 for the ICER of 54.1, obtained by the regression analysis presented in the ISPOR New Orleans 2013. **CONCLUSIONS:** Our approach can offer a simple and science-based method to estimate boundaries for any ICER. It would be useful for negotiations and decisions in value-based pricing in which a range of ICER must be considered beyond a single threshold ratio.

PRM120

BIAS WHEN USING PROPENSITY SCORE METHODS TO ADJUST FOR COVARIATES THAT ARE NOT CONFOUNDERS

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OBJECTIVES: High-dimensional propensity score (PS) methods have been used in health care claims data to improve control of confounding by adjusting for a large number of covariates that may be proxies for unobserved factors. We have previously shown that PS models are biased for non-linear link functions when confounders were included. We conducted a simulation study to understand whether inclusion of covariates that are not confounders may also bias the association by estimating Monte Carlo mean bias, relative efficiency (RE) and coverage probability (CP) of log odds ratios when covariates only related to the exposure or only related to the outcome were included. **METHODS:** We conducted 1000 Monte Carlo simulations, and estimated effect of exposure using logistic regression models. The propensity score was included in the logistic model as a linear predictor or as a smoothed covariate using restricted cubic splines. Simulations were conducted for scenarios including 5, 15, and 25 covariates. **RESULTS:** Using the PS with 25 covariates related only to the binary exposure, Monte Carlo bias, standard error (SE), RE and CP were -0.002, 0.015, 1.34, and 0.94 when the PS was included as a smoothed covariate, and –0.002, 0.015, 1.31, and 0.94 when the PS was included as a linear covariate. The bias, SE, RE and CP for 25 covariates related to the binary outcome were 0.307, 0.096, 21.6, and 0 when the PS was included as a linear covariate. Bias tended to increase with more covariates. **CONCLUSIONS:** We observed minimal bias when using PS models where covariates were related only to the exposure, but substantial bias when the covariates were related to the outcome. PS models may not be appropriate for logistic models because these models do not adequately deal with errors in the outcome due to the covariate.

PRM121
EFFICIENT ESTIMATION OF THE INCREMENTAL COST-EFFECTIVENESS RATIO (ICER) USING A NEW PERSPECTIVE
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OBJECTIVES: To develop and test a new method of estimating the ICER utilizing the harmonic mean. **METHODS:** A statistically-efficient point and 95% confidence interval (CI) estimator of the ICER was derived that utilized the harmonic mean of costs and effects, hence applying the inverse of the mean of the inverses for use in statistical summarization. An additional correction factor developed through computational intelligence was also incorporated to capture existing information from the usual bootstrap ICER estimator. A simulation study of 1111 replications with 999 bootstrap resamples each utilizing Matlab R2012b was undertaken across illustrative positive and negative correlation structures of costs and outcomes for varying sample sizes of treatment and referent groups. Results were presented as relative efficiencies for point estimators, while coverage probability, coverage error, length, left and right bias, and relative bias were presented for the 95% CI. **RESULTS:** Compared to the usual bootstrap approach, optimal methods based upon the harmonic mean yielded point estimates with greater relative efficiency across all analytic scenarios, ranging from 103.22% to 111.03%. The 95% CI coverage error was also consistently lower, deviating from the population value by 0.0005 to 0.0257 versus the usual bootstrap range of 0.0031 to 0.0302. Thus, an improved shortening of the CI length was found across all cases. The maximum relative bias of the new estimator was 0.7714 versus 0.2703, which reflected a somewhat higher left bias and lower right bias among positive correlation structures, and a greater right bias and lesser left bias among negative correlation structures. **CONCLUSIONS:** The new approach to estimate the ICER that utilized the harmonic mean allowed for more statistically-efficient point estimation. The 95% CIs presented with less coverage error and shorter lengths, though typically at the cost of a potential increase in relative bias.

PRM122
SURVIVAL CROSSOVER ADJUSTMENT AND COST EFFECTIVENESS ANALYSIS: AN EMPIRICAL AND METHODOLOGICAL REVIEW WITH APPLICATION
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OBJECTIVES: First, to summarize the methodological literature on the correction of overall survival for the impact of crossover. Second, to examine and compare the use of these statistical methods in cost-effectiveness analyses (CEAs). Third, to apply recommended statistical methods to correct overall survival in a clinical trial that included crossover. **METHODS:** Medline, Embase, NHSEED and HEED databases, along with grey literature were searched for methodological evidence on the appropriate use of survival adjustment, including but not limited to, Inverse Probability of Censor Weighting (IPCW) and Rank Preserving Structural Failure Time Modelling (RPSFT). In addition, empirical CEAs that applied survival adjustment were identified and reviewed. The appropriate methods were applied to a trial with crossover to compare IPCW, RPSFT, intention to treat (ITT) and per protocol (PP) analysis. **RESULTS:** The choice of IPCW or RPSFT depends on six factors: common treatment effect, true treatment effect, crossover percentage, disease severity, time dependence of treatment effect, and crossover mechanism. Nine placebo-controlled CEAs that applied survival adjustment were identified: two studies used one method without comparison, one study incorporated censor weighting for a meta-analysis, five studies reported one method and compared to either ITT or PP analysis, one as the primary analysis and four as sensitivity analysis. Only one study reported a comparison of multiple methods, IPCW and RPSFT. Empirically, PP, RPSFT and IPCW produce lower hazard ratios than ITT. Ranking of PP, RPSFT and IPCW varied by the factors. None of the six factors were discussed thoroughly in the empirical results. Based on the trial, all patients that crossed-over survived which violates the assumptions of common treatment effect for RPSFT and different disease severity for IPCW and RPSFT. **CONCLUSIONS:** Applying the six factors guides the a priori assessment of appropriate choice of crossover method. In this case, neither IPCW or RPSFT were appropriate.

PRM123
A MICROSOFT-EXCEL BASED TOOL FOR RUNNING AND CRITICALLY APPRAISING SIMPLE NETWORK META-ANALYSES USING WINBUGS – AN OVERVIEW AND APPLICATION
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OBJECTIVES: The role of network meta-analyses has increased dramatically in recent years. WinBUGS has been the most widely used software to conduct network meta-analyses. However, the learning curve for using WinBUGS to conduct network meta-analyses successfully can be daunting, especially for new users. Further, critically appraising network meta-analyses conducted in WinBUGS is challenging given the limited data analysis and graphical output fromWinBUGS, thus network meta-analyses often rely on different software packages. The objective is to develop a tool which 1.) makes running network meta-analyses more accessible to novice WinBUGS users; and 2.) facilitates a more transparent and efficient critical appraisal of network meta-analyses. **METHODS:** We developed a freely available Microsoft-Excel based tool, programmed in Visual Basic for applications within Excel, which provides an interface for conducting a network meta-analysis using WinBUGS from within Microsoft Excel. This tool allows the user to modify assumptions and to run the network meta-analysis, and results are returned to an Excel spreadsheet. The tool displays the data, evidence networks, forest plots, rankograms, and inconsistency plots all entirely within Microsoft Excel. **RESULTS:** We demonstrate the application of our freely available Microsoft-Excel based tool using an example of a network meta-analysis of anti-platelet agents in patients scheduled for percutaneous coronary inteventions. **CONCLUSIONS:** Use of this freely available Microsoft-Excel based tool successfully demonstrated its ability to make running network meta-analyses more accessible to novice WinBUGS users, and facilitate more transparent critical appraisal of network meta-analyses.

PRM124
MATCHING WITH MULTIPLE CONTROL GROUPS TO MAXIMIZE USE OF REGISTRY DATA FROM PATIENTS WITH SCHIZOPHRENIA
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OBJECTIVES: In order to examine comparative research questions using data from a naturalistic, observational study (REACH-OUT) of adult patients with schizophrenia, non-traditional methods were needed. This abstract describes the use of multiple control groups to maximize inclusion of paliperidone palmitate (PP) patients in REACH-OUT who would otherwise be excluded from analysis due to poor propensity score matching with registry controls (patients receiving oral atypical antipsychotics (OAT)). The matched cohorts (PP and combined OAT) will be used in future resource use comparisons. **METHODS:** Because matching on propensity of PP treatment did not yield an adequate number of matched registry controls, a secondary set of OAT controls was extracted from MarketScan® claims data. PP patients unmatched to registry controls were matched to claims controls using a 1:1 propensity score matching. Post-match baseline characteristics for the PP and combined OAT cohort were examined using descriptive statistics. Outcomes from the claims-based control group will be adjusted for source bias based on 500 simulations, according to the Stuart-Rubin (S-R) methodology. **RESULTS:** Out of 354 PP with non-missing baseline data, 190 were matched to registry controls and the remaining 164 were matched to the supplemental control group. The final matched PP and OAT cohorts were balanced in observed attributes such as age (41.4 years vs. 42.0, p=0.552), gender distribution (70.3% vs. 65.5% male, p=0.171), ≥1 baseline hospitalization (29.7% vs. 34.5%, p=0.171), and ≥1 baseline ER visit (31.1% vs. 35.6%, P=0.202), respectively. Initial S-R simulations suggest outcomes for the supplemented control group are similar to the cohort of all REACH-OUT controls (e.g., 6 month admission rates, 18.9% and 22.6%, respectively). **CONCLUSIONS:** Use of multiple control groups permitted successful propensity score matching of all registry PP patients allowing for greater power, better precision, and increased external validity in the forthcoming analysis of the treatment effect of PP.

RESEARCH ON METHODS – Study Design

PRM125
RISK ON USING LOGISTIC REGRESSION TO ILLUSTRATE EXPOSURE-RESPONSE RELATIONSHIP OF INFECTIOUS DISEASE
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OBJECTIVES: Logistic regression is widely used to assess the likelihood of an infectious disease as a function of a risk or exposure factor (and covariates), to illustrate the exposure-response relationship. However, because the exposure of patients with infectious disease is an intricate net instead of independent factors, the statistical power of logistic regression may be compromised leading to an inaccurate conclusion. Therefore, this study aims to examine the statistical power of logistic regression using simulated data of infectious disease. **METHODS:** A dynamic human immunodeficiency virus (HIV) infection was simulated among 10000 individuals with 1% initial prevalence and 7% target prevalence. Monte Carlo simulation method was used to examine the statistical powers of regular logistic regression (grouping sexual partners into 0-2, 3-5, 6-8, 9-11, 12-14 and ≥15), transformed logistic regression (using log[1+number of sexual partners]) and negative binomial regression on estimating the risk of HIV infection along with increasing number of unprotected sexual partners. **RESULTS:** Regular logistic regression had poor statistical power and overestimated the odds ratio (OR) when the number of sex partner was more than 11 (power was 78% for 12-14 partners and only 4% for over 14 partners). Transformed logistic regression overstated the odds ratio even while the number of sex partner was small. Negative binomial regression had 100% power finding the association between HIV infection and the number of sexual partners, yet it was not available to provide odds ratio. **CONCLUSIONS:** Due to the diverse distribution of exposure in infectious disease (negative binomial), evaluations that include logistic regression, to explore the exposure-response relationship, provide improved rigor to base decisions.

PRM126
BURDEN OF NARCOLEPSY DISEASE (BOND) STUDY: VALIDATION OF USING A SINGLE DIAGNOSIS CODE TO DEFINE PRESENCE OF AN ORPHAN CONDITION IN MEDICAL CLAIMS DATA
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OBJECTIVES: A US medical claims-based analysis was designed to evaluate burden of illness associated with narcolepsy, a chronic, non-progressive disease often presenting early in life. Because diagnostic testing for narcolepsy is not normally repeated, objective evidence of a diagnosis would be absent for many patients in a time-limited data set. Therefore, internal validation of a study population selected using diagnosis codes was performed. **METHODS:** Within the 5-year data collection period (2006 through 2010), 9312 continuously insured adult patients were